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Title: Stressful life events and Catechol-O-methyl-transferase (*COMT*) gene in bipolar disorder

Running head: Life events and *COMT* in bipolar disorder

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Abstract

Background: A small body of research suggests that gene-environment interactions play an important role in the development of bipolar disorder. The aim of the present study is to contribute to this work by exploring the relationship between stressful life events and the *COMT* Val¹⁵⁸Met polymorphism in bipolar disorder. **Methods:** A total of 482 bipolar cases and 205 psychiatrically healthy controls completed the List of Threatening Experiences Questionnaire. Bipolar cases reported the events experienced 6 months before their worst depressive and manic episodes; controls reported those events experienced 6 months prior to their interview. The genotypic information for the *COMT* Val¹⁵⁸Met variant (rs4680) was extracted from GWAS analysis of the sample. **Results:** The impact of stressful life events was moderated by the *COMT* genotype for the worst depressive episode using a Val dominant model (adjusted Risk Difference = 0.09, 95% confidence intervals 0.003-0.18, p=0.04). For the worst manic episodes no significant interactions between *COMT* and stressful life events were detected. **Conclusions:** This is the first study to explore the relationship between stressful life events and the *COMT* Val¹⁵⁸Met polymorphism focusing solely on bipolar disorder. The results of this study highlight the importance of the interplay between genetic and environmental factors for bipolar depression.

Introduction

Stressful life events such as bereavement and divorce, have been associated with illness (Johnson, 2005) and episode onsets (Hosang et al., 2012) as well as symptom exacerbation (Hosang, Uher, Maughan, McGuffin, & Farmer, 2012; Johnson et al., 2008) in bipolar disorder. But not everyone who experiences stressful life events goes on to develop this illness or relapses (Johnson, 2005). Given the variation in response to stress, much research in bipolar disorder has been dedicated to exploring stress vulnerability factors, which include cognitive style (Reilly-Harrington, Alloy, Fresco, & Whitehouse, 1999) and social support (Cohen, Hammen, Henry, & Daley, 2004). But genetic stress sensitivity in bipolar disorder has received less attention and calls for further research in this area have been made (Uher, 2014). One such study found that the *BDNF* Val⁶⁶Met polymorphism moderated the impact of stressful life events in bipolar disorder, but only for depressive rather than manic episodes (Hosang et al., 2010a). The aim of the current study is to explore the relationship between stressful life events and the Val¹⁵⁸Met polymorphism in the *catechol-O- methyltransferase* [*COMT*] gene.

Given that dopamine imbalance or dysregulation has been implicated in the pathogenesis of bipolar disorder (Berk et al., 2007), *COMT* has been researched as a candidate gene for this illness since it is involved in dopamine metabolism (Egan et al., 2001). Dopamine influences prefrontal cortex function, which is commonly impaired in bipolar disorder (Zalla et al., 2004). The prefrontal cortex is involved in executive functions, such as working memory as well as regulation of mood states (Strakowski, Delbello, & Adler, 2012). Research shows that stress impacts dopamine levels that may in turn influence prefrontal cortex functioning (Berk et al., 2007), potentially leading to the expression of bipolar disorder. A functional polymorphism contained in the *COMT* gene, Val¹⁵⁸Met, results

in the substitution of Valine [Val] to Methionine [Met] (Egan et al., 2001). The Val allele is associated with greater *COMT* enzyme activity and thus increased metabolism of dopamine reducing extracellular cortical dopamine concentrations (Egan et al., 2001) and prefrontal cortex functioning (Egan et al., 2001) relative to the Met variant. The relationship between *COMT* Val¹⁵⁸Met and bipolar disorder is inconsistent, with some studies finding an association with the Val variant (Benedetti et al., 2011) and others with the Met allele (Zhang et al., 2009). Null findings have also been reported concerning this association (Hosák, 2007), and genome-wide association studies [GWAS] for bipolar disorder have failed to identify this polymorphism (Craddock & Sklar, 2013). The lack of consideration of environmental factors in these studies are likely to explain their disparate findings (Moffitt, Caspi, & Rutter, 2005).

COMT Val¹⁵⁸Met has been implicated in stress vulnerability in the context of psychosis and depression, but to date no study exists which focuses specifically on bipolar disorder. Several studies report that the Val variant of this polymorphism significantly moderates the impact of childhood trauma and daily stress in psychosis (Ramsay et al., 2013; Simons et al., 2009; Stefanis et al., 2007) and depression (Drury et al., 2010). In contrast, other studies have found significant interactions with the Met variant (Collip et al., 2011; Comasco et al., 2011) or failed to detect an interaction altogether (Evans et al., 2009). One possible reason for the mixed results is the lack of consistency with the genetic models used in the analyses ranging from Val recessive (Val/Val compared to Met/Met and Val/Met) to Met recessive (Met/Met compared to Val/Val and Val/Met), which can influence the results. To better elucidate the *COMT*-stress interaction in psychopathology all three genetic models should be tested (i.e. additive, recessive and dominant).

A study of particular interest was conducted by Mandelli and colleagues (Mandelli et al., 2007) which used a sample of people diagnosed with either bipolar disorder or major depression, and found a significant interaction between stressful life events and *COMT* Val¹⁵⁸Met in illness onset. The inclusion of people with bipolar disorder in this study provided a unique contribution to the field, but several aspects of this work warrant further investigation. First, the interaction between stressful life events and *COMT* was not examined in bipolar disorder separately but rather the type of diagnoses was controlled for in the analyses. Thus it is not clear whether this gene-environment interaction [GxE] is relevant to bipolar disorder specifically. Second, in this study there was no distinction between bipolar depressive and manic episodes, rather these were examined together in terms of illness onset. The distinction between these two episode types is crucial given that they have been related to differential risk factors (Cuellar, Johnson, & Winters, 2005; McGuffin et al., 2003).

To address the methodological limitations and gaps in the literature, the current study aimed to investigate the interaction between stressful life events and *COMT* Val¹⁵⁸Met in bipolar disorder examining depressive and manic episodes separately, and testing all three genetic models.

Method

Participants

A total of 482 participants with bipolar disorder and 205 psychiatrically healthy controls were included in this study and were drawn from the Bipolar affective disorder Case Control study [BaCCs] (Gaysina et al., 2009). Participants with bipolar disorder were mainly recruited from psychiatric outpatient clinics with the remainder enlisted through self-help groups and media advertisement in the UK. All of the participants with bipolar disorder met DSM-IV criteria for bipolar I or bipolar II disorder. Participants were excluded if their bipolar episodes only occurred in relation to substance misuse, a physical disorder or if they had a personal or family history of schizophrenia.

Controls were recruited through newspaper advertisement and from staff working at King's College London. The exclusion criteria for the controls were personal or family (among first degree relatives) history of any psychiatric illness. A significant correlation between age at index period and the number of stressful life events recorded has been previously reported in this sample (Hosang et al., 2010b). In order to prevent age at interview confounding the results, controls were selected to match the mean age (± 1 standard deviation) of the bipolar cases at the time of their worst affective episodes (i.e. 26–49 years).

All participants were aged 18 years and over, Caucasian (to minimize artifacts due to population stratification) and provided informed consent to participate in the study. Ethical approval was obtained from the Joint South London and Maudsley, and Institute of Psychiatry Research Ethics Committee. All procedures contributing to this work were conducted in accordance with the Declaration of Helsinki in 1975 (revised in 2008), and the

ethical standards of the national and institutional committees on human experimentation.

Measures

Clinical assessment. The Schedule for Clinical Assessments in Neuropsychiatry, Version 2.1 [SCAN] interview (Wing et al., 1990) was administered to all bipolar participants to determine a formal lifetime diagnosis of bipolar disorder. Trained research assistants retrospectively rated the presence and severity of psychopathology items for the worst depressive and manic episodes. To do this, the 4-6 week period of peak intensity of the symptoms during these episodes were identified and rated using each of the SCAN items. The computerised version of the SCAN 2.1 is built on top of the iSHELL system, which is a computer-aided personal interviewing tool produced by the World Health Organization and which provides DSM-IV operationally defined diagnoses (Celik, 2003).

Stressful life events. All participants completed the List of Threatening Experiences Questionnaire (Brugha, Bebbington, Tennant, & Hurry, 1985), which was used to record the experience of 11 different life events that occurred 6 months prior to the bipolar cases' worst depressive and worst manic episodes, and 6 months prior to interview for controls. The List of Threatening Experiences Questionnaire has been shown to capture 82.5% of the life events covered by more comprehensive life event interviews (Brugha & Cragg, 1990). Trained research assistants administered the List of Threatening Experiences Questionnaire to participants, this involved confirming the event occurred during the index period and obtaining any contextual information to help determine whether the reference event satisfied the classification of the items.

Genotyping. The genotypic data for rs4680 (*COMT* Val¹⁵⁸Met) were extracted from genome-wide genotyping for the sample with DNA extracted from blood samples. Using the Illumina Sentrix Human Hap550 BeadChip genome-wide genotyping was performed on both the bipolar cases and controls. Data extraction was carried out by the Illumina® Beadstudio software from data files created by the IlluminaBeadArray reader. On completion of the genotyping the data were subject to a number of quality control tests. Various parameters were considered under quality control tests including sample contaminations, duplications, and mis-identification using the genome-wide identity-by-descent estimation. Inconsistent samples were removed (see Xu et al., 2014; Zai et al., 2015) for more details. The *COMT* Val¹⁵⁸Met genotypic distribution (see **Table 1**) was in Hardy Weinberg Equilibrium ($\chi^2(1)=1.61$, $p=0.21$) and did not differ between the bipolar cases and controls ($\chi^2(2)=2.08$, $p=0.35$).

Population stratification. Given that there are ethnic and ancestry differences in the association between *COMT* Val¹⁵⁸Met and bipolar disorder (Zhang et al., 2009) care was taken to control for the effect of population stratification. The first principal component from the Principal components analyses [PCA] was used to control for population stratification effects. PCA was conducted for the original GWAS of BACCs (Scott et al., 2009).

Analyses

Group differences were tested using chi-square, Cuzick's non-parametric trend test and t-tests. Following recommendations for GxE studies (Uher et al., 2011), the main effects and interactions between stressful life events and *COMT* Val¹⁵⁸Met on the presence/absence of bipolar disorder were examined using generalized linear models with

binomial distribution and identity link function specified (Wacholder, 1986) to estimate risk differences [RD] with 95% confidence intervals [CI]. These analyses were adjusted for gender, age at index period and the population stratification principal components variable; tests were conducted separately for the worst depressive and manic episodes. All three genetic models were tested: additive (0=Met/Met, 1=Val/Met, 2=Val/Val), Val dominant (0=Met/Met, 1=Val/Met and Val/Val) and Val recessive (0=Met/Met and Val/Met, 1=Val/Val). All analyses were conducted using STATA version 14.

Results

Data were available for 482 participants with bipolar disorder and 205 psychiatrically healthy controls. The bipolar cases had an average age of illness onset of 22.01 years (SD=17.80), with 12.53 (SD 20.25) mean number of depressive episodes and 11.30 (SD 20.13) manic episodes. The sample characteristics are presented in **Table 1**, which show that significantly more females were included in the bipolar cases group compared to controls ($\chi^2 (1)=4.07$, $p=0.044$). Bipolar cases reported significantly more life events 6 months prior to their worst episodes compared to controls for the 6 months before their interview (worst depressive episode: $z=5.20$, $p\leq 0.001$; worst manic episode: $z=5.01$, $p\leq 0.001$). The three most frequently reported life events reported by bipolar cases prior to their worst mood episodes were: item 1, personal illness, injury or assault (worst depressive episode: 20%; worst manic episode: 17%); item 5, marital separation or break-up of a romantic relationship (worst depressive episode: 21%; worst manic episode: 20%) and item 6, serious problem with close friend, neighbour or relative (worst depressive episode: 22%; worst manic episode: 27%).

The main and interactive effects of stressful life events and *COMT* Val¹⁵⁸Met polymorphism are presented in **Table 2**. All 3 genetic models were tested but showed no significant main effect of *COMT* on bipolar disorder (see **Table 2**). The number of life events reported prior to the worst depressive (adj.RD=0.09, 95% CI 0.05-0.13, $p\leq 0.001$) or manic (adj.RD=0.09, 95% CI 0.05-0.13, $p\leq 0.001$) episodes were significantly associated with bipolar disorder. Using the Val dominant genetic model, a significant interaction between *COMT* Val¹⁵⁸Met and stressful life events on bipolar disorder was detected for the worst depressive episode (adj.RD=0.09, 95% CI 0.003-0.18, $p=0.04$). Further examination of this interaction showed that the association between stressful life events and bipolar disorder is significant

and higher for those in the Val dominant group (adj.RD=0.11, 95% CI 0.07-0.17, $p \leq 0.001$) compared to those with the Met/Met genotype (adj.RD=0.02, 95% CI -0.05-0.10, $p=0.57$).

Using an additive model the interaction between life events and *COMT* showed a trend towards significance for the worst depressive episode (adj.RD=0.05, 95% CI -0.01-0.10, $p=0.08$). No significant GxE were found using the Val recessive model.

Discussion

The results of this investigation found a significant interaction between *COMT* Val¹⁵⁸Met and stressful life events in adulthood in bipolar disorder for depressive episodes using a Val dominant genetic model. To our knowledge this is the first study to investigate this GxE solely in bipolar disorder and contributes to the conflicting literature on *COMT*-stress interactions in psychopathology. The findings reported here are consistent with that of previous studies which have found interactions between the Val allele of *COMT* Val¹⁵⁸Met and different types of stress in psychosis (Ramsay et al., 2013; Simons et al., 2009) and depression (Drury et al., 2010). But there is also evidence of this GxE using the Met variant (Collip et al., 2011; Mandelli et al., 2007). Conceptual and methodological differences between the studies may explain the divergent results. Examples include differences in types of stress examined (e.g., stressful life events in adulthood or childhood adversity), stress measurement (questionnaire or interview) and outcome variables (e.g., symptoms or clinical disorder). These differences have been shown to play a pivotal role in the detection of other GXEs (e.g., *5-HTTLPR* x stress in depression) (Uher & McGuffin, 2008). Clearly more research is needed to clarify the relationship between stress and *COMT* in bipolar disorder and psychopathology more broadly.

The findings of this study provide a novel contribution to the field of GxE in bipolar disorder, helping to show that genetic stress-vulnerability for this illness is likely to involve multiple genes. For example, stressful life events have been shown to significantly interact with the Met variant of *BDNF* Val⁶⁶Met (Hosang et al., 2010a) and the current study indicates that they interact with the Val allele of *COMT* Val¹⁵⁸Met in bipolar disorder. However, these results should be considered preliminary because they just reached conventional levels of significance and were not corrected for testing of the three genetic

models. Clearly the results of this study warrant replication, but future research should also explore GxEs focusing on different types of stressors such childhood adversity (e.g., childhood abuse and neglect) as well as multiple interactions between genes and environments (eg. gene-gene-environment interactions and environment-environment-gene interactions). For example, one study (Ira et al., 2014) found that individuals exposed to low maternal care as a child (childhood adversity) and who experienced stressful life events in adulthood (proximal stress) reported more psychotic symptoms, and this relationship was strongest amongst the Val/Val *COMT* group. Similar work is needed in the field of bipolar disorder to build a more comprehensive aetiological model that better reflects the complex dynamic between the environment and genetic factors.

The results from this study are clinically relevant as they may help to identify individuals with bipolar disorder at greater risk of relapse when exposed to stress based on their *COMT* genotype, although more work is needed before such identification methods can be implemented. Furthermore, according to the ‘differential susceptibility’ hypothesis individuals who are genetically sensitive to adverse experiences, such as stressful life events (e.g., Val carriers of *COMT* Val¹⁵⁸Met) are generally sensitive to their environments and thus may benefit most from positive experiences (e.g., good social support) (Belsky & Pluess, 2009). One study of particular relevance showed that panic disorder patients with the Val variant of the *COMT* polymorphism showed greater reductions in anxiety symptoms after receiving cognitive behavioural therapy relative to the Met/Met group (Lonsdorf et al., 2010). Such findings need to be extended to bipolar disorder especially since the outcome of such work would have implications for targeting of similar treatments.

There are a number of methodological strengths to this study including the separate examination of bipolar depressive and manic episodes in relation to the interaction with stressful life events and *COMT* since there is evidence that these episode types are associated with differential risk factors (Cuellar et al., 2005; McGuffin et al., 2003). The current investigation is also the first to test all three genetic models in order to determine which model is most pertinent to this GxE. The lack of consideration of the different genetic models is hypothesized to explain some of the mixed findings in the literature. But several limitations need to be considered when interpreting the findings from the present investigation.

First, the stressful life events data are vulnerable to retrospective reporting biases (e.g., normal forgetting) as participants with bipolar disorder were asked to recall events they experienced 6 months preceding their worst mood episodes, which may have occurred some years prior to the study assessment. Future studies should adopt prospective longitudinal approaches to address this potential bias.

Second, using a life event questionnaire has some limitations, including the participants' subjective interpretation as to what counts as an instance of a certain item and the misdating of events (Spence et al., 2015). Life event interviews are comprehensive and likely to be the optimum way of measuring stressful life events, but they are time and labour intensive and thus expensive (Spence et al., 2015) especially when applied to the large samples needed to detect GxEs (Moffitt et al., 2005). Questionnaires are attractive and often considered more suitable to large studies as they are cheaper than interviews because they are quick and easy to complete. In the current investigation we chose to compromise by using a researcher-administered questionnaire that attempts to surmount dating and contextual issues related to using a self-report questionnaire with the added benefit of

reducing the time and expense of more lengthy interviews. Nonetheless, the findings of this study should be replicated using life event interview measures to address this issue.

Finally, all participants were Caucasian to control for the effects of population stratification, but this means it is unclear with the results are generalizable to other ethnicities. Future studies should explore the interaction between stressful life events and *COMT* in bipolar disorder using participants from other ethnic groups.

To summarise, this is the first study to solely focus on bipolar disorder and examine the relationship between *COMT* and stressful life events. The results showed a significant interaction between stressful life events and *COMT* Val¹⁵⁸Met for bipolar depressive episodes using a Val dominant model.

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Table 1. Sample characteristics for participants with bipolar disorder and psychiatrically healthy controls.

Characteristics	Bipolar cases N=482 N (%)	Controls N=205 N (%)	Statistic	P-value
Female	321 (67)	120 (59)	$\chi^2 (1)=4.07$	0.044
Age at index period in years [mean (SD)] ^a	WDE: 37.4 (11.78)	34.7 (7.36)	t(673)=2.98	0.002
	WME: 37.3 (11.35)	34.7 (7.36)	t(673)=3.05	0.002
Number of life events reported				
Worst depressive episode				
0	174 (36)	106 (52)		
1	130 (27)	66 (32)		
2 or more	178 (37)	33 (16)	z=5.20	p≤0.001
Worst manic episode			z=5.01	p≤0.001
0	177 (37)	106 (52)		
1	131 (27)	66 (32)		
2 or more	174 (36)	33 (16)		
COMT genotypic groups				
Val/Val	106 (22)	55 (27)		
Val/Met	230 (48)	95 (46)		
Met/Met	146 (30)	55 (27)	$\chi^2(2)=2.08$,	p=0.35

^a bipolar cases had two index periods, 6 months before their worst depressive and manic episodes. Controls had one index period, 6 months preceding their interview.

Abbreviations: WDE, worse depressive episode; WME, worst manic episode; COMT, Catechol-O-methyltransferase; Val Valine; Met, Methionine; N, number of participants; SD, standard deviation; P,

probability due to chance.

Table 2. Main and interaction effects between *COMT* Val¹⁵⁸Met and stressful life events in relation to bipolar disorder cases status.

	Adjusted RD ^a	95% CI		P-value
		Lower	Upper	
<i>Main effects</i>				
Stressful life events:				
Worst depressive episode	0.09	0.05	0.13	≤0.001
Worst manic episode	0.09	0.05	0.13	≤0.001
COMT Genetic models:				
Additive genetic model	-0.02	-0.07	0.03	0.50
Val recessive genetic model	-0.03	-0.12	0.06	0.49
Val dominant genetic model	-0.02	-0.10	0.06	0.66
GxE: Worst depressive episode				
Additive model x SLEs	0.05	-0.01	0.10	0.08
Val recessive model x SLEs	0.04	-0.05	0.13	0.41
Val dominant model x SLEs	0.09	0.003	0.18	0.04
GxE: Worst manic episode				
Additive model x SLEs	0.03	-0.03	0.09	0.33
Val recessive model x SLEs	0.01	-0.09	0.11	0.85
Val dominant model x SLEs	0.06	-0.03	0.15	0.18

^a Results were adjusted for the effects of gender, age at index period and population stratification.

Abbreviations: COMT, Catechol-O-methyltransferase; RD, relative risk; CI, confidence interval; Val, valine; SLEs, stressful life events; GxE, gene-environment interactions; P, probability due to chance.

Figure legend

Figure 1. Proportion of individuals with bipolar disorder by number of stressful life event reported 6 months before the index period and *COMT* genotype. The y-axis presents the probability of having bipolar disorder by the number of stressful life events and *COMT* Val156Met genotype (Met/Met, Val/Met, and Val/Val) for the worst episodes of depression (Panel A) and mania (Panel B). The number of individuals included in each subgroup is provided above each bar.



